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REVIEW

Strategies to increase the resectability of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is best treated by liver transplantation, but the applicability of transplantation is greatly limited. Tumor resection in partial hepatectomy is hence resorted to. However, in most parts of the world, only 20%-30% of HCCs are resectable. The main reason for such a low resectability is a future liver remnant too small to be sufficient for the patient. To allow more HCC patients to undergo curative hepatectomy, a variety of ways have been developed to increase the resectability of HCC, mainly ways to increase the future liver remnants in patients through hypertrophy. They include portal vein embolization, sequential transarterial chemoembolization and portal vein embolization, staged hepatectomy, two-staged hepatectomy with portal vein ligation, and Associating Liver Partition and Portal Vein Ligation in Staged Hepatectomy. Herein we review, describe and evaluate these different ways, ways that can be life-saving.

Key words: Hepatocellular carcinoma; Hepatectomy; Portal vein ligation; Associating Liver Partition and Portal Vein Ligation in Staged Hepatectomy; Portal vein embolization

Core tip: There are different ways to increase the resectability of hepatocellular carcinoma by increasing the volume of the future liver remnant (FLR) through hypertrophy. Portal vein embolization features the the embolization of the ipsilateral side of the portal vein which supplies the liver lobe harboring the tumor, either in an open or percutaneous manner. Sequential transarterial chemoembolization and portal vein embolization is a way to augment the effect of portal vein embolization and prevent tumor progression. Staged hepatectomy is mainly for liver tumors with bilobar involvement and colorectal liver metastasis and is often aided by effective adjuvant chemotherapy. Its aim is to strike a balance between complete tumor removal and preservation of the FLR. Two-staged hepatectomy with portal vein ligation is also mainly for liver tumors with bilobar involvement and colorectal liver metastasis. In the first-stage operation, tumor in the liver portion which is designated as the FLR is cleared, and portal vein ligation is performed. The liver parenchyma is transected

only in the second-stage operation. Associating Liver Partition and Portal Vein Ligation in Staged Hepatectomy is used to speed up hypertrophy in the hope that the FLR will grow large enough for a safe hepatectomy before tumor progression occurs. It features right portal vein ligation and in-situ splitting of the intended transection surface down to the inferior vena cava. In the first-stage operation, the anterior approach is encouraged and the Pringle maneuver is discouraged, and the hilar plate is left untouched.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the most common primary liver malignancy[1,2]. Most cases of HCC in Asia are related to hepatitis B, which is prevalent in the region[3]. The best treatment for HCC is liver transplant because it removes both the tumor and the diseased liver, and a 5-year post-transplant survival rate of > 70% is expected[4-7]. Unfortunately, its applicability is limited by the shortage of liver grafts[8]. Moreover, only patients who have HCC within selection criteria (*e.g.*, the Milan criteria[9], the University of California, San Francisco criteria[10] are eligible for liver transplant. A study reported that for patients with HCC within the Milan criteria, the 5-year survival rate was 81% with living donor liver transplant and 72.8% with partial hepatectomy[11]. In the face of perpetual liver graft shortage, hepatectomy remains an important curative measure as it can achieve a satisfactory survival outcome.

Hepatectomy has been evolving and is getting more technically challenging as surgeons are pushing limits. They are trying to operate on HCCs larger and larger and with more and more nodules, but a R0 resection is always the ultimate goal. The applicability of hepatectomy is often limited by an inadequate future liver remnant (FLR) or a marginal liver, especially in patients with underlying hepatitis or cirrhosis. The success of hepatectomy depends on many factors, which include status of the tumor, the patient's clinical status and underlying liver function, and the size of the FLR of the patient[12-14]. Aggressive hepatectomy may still be beneficial for patients who have advanced HCC with large or multiple tumors or intrahepatic venous invasion if they are properly selected[15]. Curative hepatectomy is the first-line treatment for HCC at many centers. The resectability of HCC often rises with the volume of the FLR, and therefore different measures are employed for increasing such volume. Moreover, a larger FLR would probably mean better overall and disease-free survival.

SURGICAL RESECTION

In the management of HCC, liver resection for tumor clearance is the first-line curative treatment for patients with preserved liver function[11,14,16]. Major hepatectomy can be performed safely nowadays with careful patient selection[12,14], better understanding of the liver anatomy[17], improvement of surgical techniques, and advances of surgical instruments. Widely adopted techniques include the hanging maneuver[18], the anterior approach for avoidance of mobilization and rupture of large tumors[19,20], the Pringle maneuver[21], and meticulous control of central venous pressure for reduction of reduce blood loss[22]. Widely employed instruments include Cavitron Ultrasound Surgical Aspirator, hydrojet[23,24], the Harmonic scalpel, LigaSure, Harmonic Ace, and Thunderbeat[25]. Although complications and perioperative mortalities still occur, the rates are acceptable[13,14,26,27]. However, major hepatectomy may not be suitable for patients with marginal liver function or a relatively small FLR. The University of Hong Kong uses indocyanine green clearance test as an important tool to assess their patients' preoperative liver function[28]. Unfortunately, there is no perfect test for the prediction of postoperative mortality[29,30]. For risk stratification for major hepatectomy, usually a combination of assessment modalities is adopted, which usually includes measurement of the disease's Child-Pugh grading, indocyanine green clearance test, renal function test by creatinine level check, and platelet count.

Location of tumors is a decisive factor in surgical planning. The amount of liver removed in hepatectomy decides the volume of the liver remnant. Major hepatectomy can only be offered to patients with an adequate FLR and adequate post-resection liver function. To avoid massive bleeding and vascular insult to the liver, preservation or reconstruction of major hepatic veins in addition to meticulous surgical skills is needed[29]. A patient's liver volume can be measured by tracing the liver contour in the cross-sectional image on computed tomography volumetry[31], and a patient's standard liver volume can be derived from his weight and height with different formulae[32,33]. The volume of his FLR can then be calculated. Patients with cirrhosis have relatively poor liver function, and thus need a larger FLR[34-37] to lower the risk of liver failure. At The University of Hong Kong, for patients who have Child-Pugh A cirrhosis and an indocyanine green retention rate $\leqslant$ 20% at 15 min, an FLR > 30% of the estimated standard liver volume is preferred for right hepatectomy, and an FLR > 35% of the estimated standard liver volume is preferred for extended right hepatectomy or right trisectionectomy. Patients who have cirrhosis and an inadequate FLR have a high risk of post-hepatectomy liver failure[37,38].

REGENERATION OF LIVER REMNANT

Different types of injury (*e.g.*, ischemia/reperfusion, resection) will induce a hypertrophic response called

the atrophy-hypertrophy complex in a liver remnant. Hypertrophy is simultaneously caused by increased endothelial shear stress, hepatocellular swelling, and activated growth factors/cytokines due to increased portal flow[39]. The idea of portal vein embolization (PVE) is to occlude a liver segment or lobule so as to bring about its ischemia[40,41] and consequent atrophy, thereby inducing hypertrophy of the part of liver not atrophied.

PVE

PVE is indicated for patients who are considered for right or extended right hepatectomy but with a relatively small FLR. By PVE, the size of an FLR can be increased. PVE features the embolization of the ipsilateral side of the portal vein which supplies the liver lobe harboring the tumor, either in an open or percutaneous manner, thereby inducing hypertrophy of the FLR[42,43]. To date, there is still no straight value on the minimum volume of an FLR which allows major hepatectomy to be performed safely. An FLR > 35% of the estimated standard liver volume has been recommended for patients with cirrhosis, steatosis, or chronic hepatitis[28,36,37,44-48]. PVE is rarely required before extended left hepatectomy or left trisectionectomy, since the right posterior section usually constitutes about 30% of the total liver volume[49,50]. The technique for embolizing the segment-4 portal vein is crucial; if the vein is not properly blocked, suboptimal hypertrophy may results.

Liver volume assessment after PVE

The FLR volume will be reassessed 4-8 wk after PVE[51,52]. Rapid growth of the FLR is anticipated in the first 3-4 wk. Generally, an 8%-30% enlargement over 2-6 wk is expected[43,52-55]. Hypertrophy is usually slower in the presence of cirrhosis[56]. Studies comparing major hepatectomy with and without preceding PVE reported that comparable and even superior long-term outcomes were achieved with PVE[45,57-63]. With PVE, patients who would have been considered inoperable in the past because of their small FLR have the option of hepatectomy with reasonable long-term surgical outcomes.

Complications of PVE

PVE can be performed in an open or percutaneous manner. Open right portal vein ligation often renders the subsequent surgery difficult due to vascular or fibrotic adhesions around the hilar structure. Open transileocolic PVE is performed with cannulation of the ileocolic vein in addition to embolization of the right portal vein in an antegrade manner or percutaneous portal vein cannulation and retrograde embolization. Ipsilateral percutaneous PVE is generally preferred because of the low invasiveness and an easier access to segment-4 portal vein branches[64-66]. Different ways of PVE all carry a risk of complication, such as main portal vein thrombosis. Prompt surgical intervention or anticoagulation is needed if the embolic agent crosses the contralateral side of the portal vein, which would cause liver failure in the case of bilateral PVE, resulting in death[67]. Hemorrhage or catastrophic bleeding at the puncture site may also occur, which also requires prompt surgical intervention. In addition, PVE induces inflammatory response near the hilar structure, which may increase the difficulty in dissection in the subsequent hepatectomy and raise the surgical risk.

SEQUENTIAL TRANSARTERIAL CHEMOEMBOLIZATION AND PVE

PVE can be given to HCC patients with underlying cirrhosis, but hepatic regeneration and thus hypertrophy of the FLR would be impaired in the presence of cirrhosis[68-70]. On the other hand, it is likely that the arterial flow increases compensatorily in segments with PVE, thereby stimulating tumor progression as HCC is a hypervascular tumor supplied by the hepatic artery blood flow[71-73]. To augment the effect of PVE and prevent tumor progression, the treatment sequential transarterial chemoembolization and PVE is used[57]. Studies comparing patients who received this treatment and patients who did not found that patients who did showed a higer rate of hypertrophy of FLR and a bigger increase in their FLR[57,58], and the rate of tumor progression was lower as tumor necrosis was evident[74]. This treatment is not without risk; it could cause ischemic parenchymal damage[75], but overall, it is feasible and safe, and it allows HCC patients who would otherwise be denied hepatectomy to undergo curative resection with reasonable postoperative 5-year overall and disease-free survival[57,58,76].

STAGED HEPATECTOMY

Staged hepatectomy is mainly for HCC with bilobar involvement and colorectal liver metastasis, and is often aided by effective adjuvant chemotherapy[77-79]. In staged hepatectomy, two or more planned hepatectomies are performed at different time to achieve a R0 resection. It is distinguished from unplanned repeat hepatectomies for recurrent disease[80]. Its aim is to strike a balance between complete tumor removal and preservation of the FLR. The chance of postoperative liver failure can be reduced if bilobar tumors are removed in a staged manner. The preserved portion of the liver should be relatively spared by the disease with sufficient FLR and adequate vascular inflow and outflow[81]. However, there is always the chance that the tumor tissue is cut across during the first-stage procedure, resulting in tumor spillage and peritoneal metastasis, and rendering the planned second-stage procedure unfeasible. Besides, tumors may grow despite temporary chemotherapy during the hepatic regenerative period, which may also preclude further operation. Repeat resection is technically demanding, as not only all the dissection

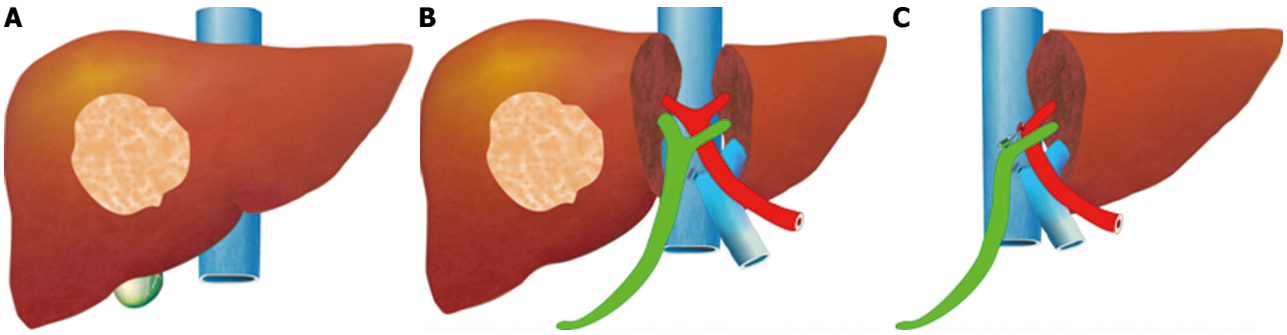

Figure 1 Associating Liver Partition and Portal Vein Ligation in Staged Hepatectomy. A: Tumor in the right liver lobe, the future liver remnant (the left liver lobe) will be small; B: In stage-1 ALPPS, the right portal vein is ligated, liver transected, inferior vena cava exposed, and gallbladder resected; C: In stage-2 ALPPS, the left liver lobe has hypertrophied, the right lobe with tumor is resected, right hepatic artery and right hepatic duct transected and ligated. Green: Bile duct; Red: Hepatic artery; Blue: Posterior inferior vena cava and anterior portal vein. ALPPS: Associating Liver Partition and Portal Vein Ligation in Staged Hepatectomy.

planes have already been disturbed, adhesiolysis can also be very difficult. Adhesiolysis near the liver hilum and the inferior vena cava is particularly challenging, as massive bleeding may occur. Staged hepatectomy for HCC was not common[79]; it was mostly for colorectal liver metastasis[78,82-85].

TWO-STAGED HEPATECTOMY WITH PORTAL VEIN LIGATION

This treatment requires two laparotomies and is also mainly for HCC with bilobar involvement and colorectal liver metastasis. In the first laparotomy, tumor in the liver portion which is designated as the FLR is cleared, and portal vein ligation is performed. Other required resection such as that of colorectal primary tumor is also done in the first laparotomy. The liver parenchyma is transected only in the second laparotomy but not in the first. The portal vein ligation is to induce hypertrophy of the FLR, allowing hepatectomy in the second-stage procedure and decreasing the risk of postoperative liver failure. Portal vein ligation has been found to be as effective as PVE[86]. However, open portal vein ligation poses the risk of adhesion formation over the hilum, which may increase the difficulty of dissection in the second-stage operation.

ASSOCIATING LIVER PARTITION AND PORTAL VEIN LIGATION IN STAGED HEPATECTOMY

For hepatectomy, one of the limiting factors is inadequate volume of the FLR. Although the aforesaid methods are effective in inducing hypertrophy of the FLR, it takes several weeks for it to reach a satisfactory volume[43]. Tumor progression may occur before the FLR is large enough for the planned hepatectomy to be conducted. If a major vessel such as the ipsilateral portal vein is invaded by tumor, the tumor will progress in terms of days and contralateral deposition and metastasis of the tumor will occur, rendering the tumor inoperable[72,73,87].

Associating Liver Partition and Portal Vein Ligation in Staged Hepatectomy (ALPPS) is one of the main surgical innovations in recent years. The procedure, which was invented by chance, was initially carried out by Dr. Hans Schlitt from Germany in an intended extended right hepatectomy for hilar cholangiocarcinoma[88]. In the surgery, palliative left hepaticojejunostomy was performed because the FLR was small, with division of the liver parenchyma along the falciform ligament and ligation of the right portal vein. On day 8 after the surgery, computed tomography was performed. To Dr. Schlitt's surprise, the left lateral section had grown enormously in size. The diseased portion of the liver was subsequently removed in another surgery. This novel technique was later termed "ALPPS"[89]. The idea of ALPPS is to speed up hypertrophy of the FLR (the left lobe or the left lateral section) by right portal vein ligation and in-situ splitting of the intended transection surface down to the inferior vena cava (Figure 1). Generally, the FLR regenerates to a volume adequate for a safe hepatectomy in days.

ALPPS was initially applied to relatively normal livers, such as in the case of colorectal liver metastasis. Later it was also applied to livers with steatosis or cirrhosis[88,90-94]. A 70% increase in FLR volume has been reported[95]. ALPPS is better than conventional PVE when the rate and the percentage of hypertrophy are concerned[96,97]. The shorter the interval between the two operations is, the less mature the adhesions would be, and hence the second operation would also be easier.

Most of the reported cases of ALPPS are on non-cirrhotic livers, and there has not been any report on the rate of hypertrophy in cirrhotic livers. However, one would anticipate that some patients would not have adequate hypertrophy of the contralateral side and hence the second stage operation is not possible. ALPPS carries certain risks. The right hepatic artery could be injured, and liver failure could occur after right portal vein ligation. The Pringle maneuver would pose a further risk of liver injury and is thus not recommended. In the first-stage operation, adoption of the anterior approach allows liver transection without mobilization of the right

lobe, thereby minimizing adhesion formation[98], and the hilar plate is left untouched so as to minimize the chance of biliary complication. Bile leakage from the transection surface can result in biloma and increases the chance of infection and thus the risk of sepsis, which may forbid the second-stage operation. ALPPS is very technically challenging and demanding, and therefore should not be carried out by inexperienced surgeons.

Indications for ALPPS

ALPPS should be carried out with a curative intent. It is indicated for patients who have a large tumor load and a marginal FLR[96], even with tumor invasion of major vessels, such as the portal vein[92]. ALPPS renders some inoperable tumors potentially operable.

Morbidity and mortality after ALPPS

Complication and mortality are inevitable with any surgery; ALPPS is no exception. Perioperative mortality rates of 12%-28% have been reported, which are overall higher than those of conventional major hepatectomy[95,96,99,100]. A complication rate high at 50% has been recorded[99,101]. Complications include ascites, bile leakage, persisting cholestasis and sepsis, wound infection, and other inflammatory and infective complications. ALPPS increases operability at the price of a heightened morbidity and mortality. Keeping morbidity and mortality at the minimum requires careful patient selection, meticulous surgical technique, and accurate decision as to proceeding to the second-stage operation or not.

The long-term outcome of ALPPS is still unknown. Long-term overall survival and disease-free survival are still pending. Further studies as well as input from different centers are required but not yet available. However, ALPPS has improved the operative rate, and it is hoped that it will improve the overall and disease-free survival of patients. Nonetheless, larger trials are needed to document its efficacy especially for those patient with HCC and background cirrhosis.

CONCLUSION

There are revolutional changes of surgical methods to increase the resectability of HCCs, and various ways to increase the volume of the FLR of patients considered for major hepatectomy have been developed. Improvement in surgical techniques also allows patients to benefit from surgical resection with safety. Treatment modalities are always evolving for the better. Hopefully, ALPPS will continue to develop and long-term results will be available in the near future.

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